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Trends in Parasitology

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Opinion

Soil-Transmitted Helminthiasis and Vitamin A Deficiency: Two Problems, One Policy

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Vitamin A deficiency (VAD) and soil-transmitted helminthiasis (STH) represent two widely prevalent and often overlapping global health problems. Approximately 75% of countries with moderate or severe VAD are coendemic for STH. We reviewed the literature on the complex relationship between STH and VAD. Treatment for STH significantly increases provitamin A (e.g., β-carotene) levels but is associated with minimal increases in preformed vitamin A (retinol). Interpretation of the data is complicated by variations in STH infection intensity and limitations of vitamin A biomarkers. Despite these challenges, increased coordination of STH and VAD interventions represents an important public health opportunity.

Trends

Available evidence suggests that soil-transmitted helminthiasis (STH) can contribute to vitamin A deficiency (VAD), although evidence on the impact of treatment for STH on VAD is inconclusive.

About 75% of countries with moderate or severe VAD are coendemic for STH.

Coordination of public health efforts to improve vitamin A status and treat STH provides synergies and public health benefits.

Expanding partnership between deworming and vitamin A supplementation efforts could help scale up deworming for preschool-age children.

VAD and STH: Two Overlapping Global Health Problems

VAD and STH represent two widely prevalent and often overlapping global health problems. Affecting the world's poorest children and responsible for significant health and economic deficits, VAD and STH have been targeted by large-scale public health interventions for decades [1–3]. Recently, the desire to align campaigns for VAD and STH has grown, driven by the potential to efficiently share delivery platforms and harness synergistic health benefits from coadministering deworming drugs with vitamin A supplementation (VAS) [4,5]. While some studies have examined the impact of vitamin A status on STH [6–8], this review explores the effect of STH on vitamin A status.

Substantial geographic overlap exists between VAD and STH in preschool-age children. An estimated 75% (93/123) of countries with moderate or severe VAD also have preschool-age children who are considered by the World Health Organization (WHO) to be at risk of STH and in need of periodic mass treatment, known as 'preventive chemotherapy' [9]. Of the 190 million children affected by VAD globally, over 95% (~181 million) live in countries where the WHO recommends mass treatment for STH [9,10] (http://www.who.int/neglected_diseases/preventive_chemotherapy/sth/en/). Figure 1 (Key Figure) displays the overlap of countries with moderate or severe VAD and where preventive chemotherapy is required for STH.

The relationship between STH and vitamin A status remains unclear, however, as do the health advantages realized by coadministering treatments. Several studies have documented adverse effects of STH on vitamin A status but others have failed to detect a significant impact [11]. Interpreting the mixed body of evidence is further complicated by the challenges involved in measuring vitamin A status and STH.

This opinion article explores the nuanced relationship between STH and vitamin A. Relevant background on both conditions is first provided, followed by closer inspection of important

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Key Figure

Global Overlap of Vitamin A Deficiency and Soil-Transmitted Helminthiasis (STH)

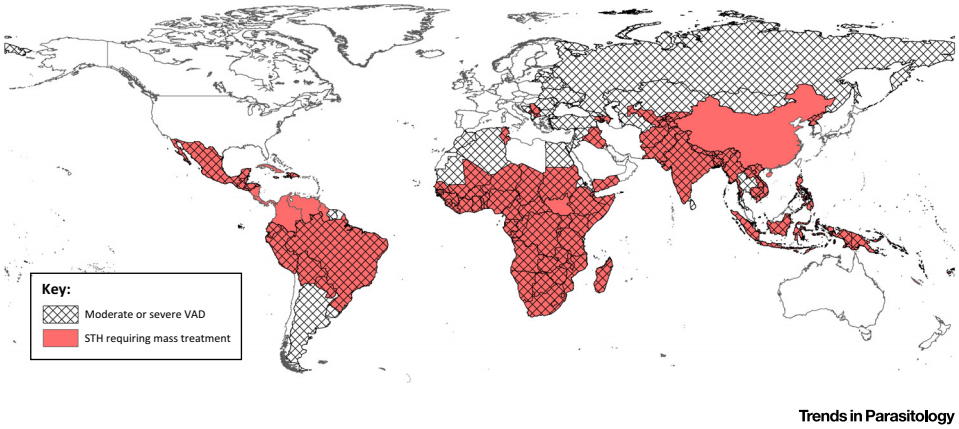

Figure 1. Shaded countries are those that require preventive chemotherapy for STH according to the WHO. Cross-hatched countries are those with moderate or severe vitamin A deficiency (VAD) according to the WHO (i.e., prevalence of VAD is 10% or higher).

methodological considerations for assessment. Next we provide a review of the key literature before discussing implications for policymakers and public health practitioners. While additional research is needed to clarify the impact of STH on vitamin A status, coordination of campaigns for the two conditions could yield greater health benefits at lower costs than if implemented separately.

Vitamin A: An Essential Micronutrient

VAD, a condition resulting from inadequate vitamin A absorption, represents a significant contributor to mortality and morbidity for children and pregnant women, with a global burden estimated at 806 000 disability-adjusted life years (DALYs) [12]. Vitamin A is an essential micronutrient needed for vision, immune function, and cell differentiation [13]. Deficiency of this nutrient can cause xerophthalmia (i.e., dryness of the eyes), which can lead to night blindness and corneal ulceration [14].

VAD is commonly assessed by measuring the concentration of retinol in blood serum or through clinical eye examinations (Table 1) [9]. The WHO recommends using the prevalence of low serum retinol in preschool-age children to define the severity of VAD as a public health program, with $\geq$10% and $\geq$20% considered moderate and severe public health problems, respectively. Indicators of vitamin A have been recently reviewed by the Biomarkers of Nutrition for Development (BOND) program [15]. High-performance liquid chromatography (HPLC) is most frequently used to assess retinol concentrations; values <0.70 μmol/l indicate deficiency and <0.35 μmol/l represents severe deficiency. Nearly all of the circulating retinol in the blood is associated with its carrier protein, retinol-binding protein (RBP). Therefore, serum RBP can be used as a surrogate measure for retinol concentration [16]. Ocular examinations reveal a range of signs of VAD, including Bitot's spots, night blindness, and impaired dark adaptation [17]. Vitamin A indicators have been reviewed in the literature [17,18].

Table 1. Vitamin A Status Indicator Summary[a]

Indicator	Assay	Classifications	Limitations
Serum retinol	HPLC	<0.70 μmol/l is considered VAD <0.35 μmol/l is considered severe VAD	Serum retinol levels are not a reliable indicator of the vitamin A liver stores Serum retinol levels show limited responsiveness to VAS
Dose response	RDR MRDR	RDR: 20% difference or greater in serum retinol concentrations pre- and post-serum retinol administration suggests low liver reserves of retinol MRDR: higher MRDR values suggest lower retinol reserves; a ratio of 3,4-didehydroretinol to retinol greater than 0.06 usually suggests low liver reserves of retinol	Cannot detect high (toxic) levels of vitamin A
Clinical signs	Visual eye inspection	Xerophthalmia can be evident from Bitot's spots (less severe) to blindness from corneal scarring (more severe); night blindness also indicates VAD	Ocular symptoms typically present only in cases of moderate-to-severe VAD
Liver sample	Liver biopsy	<0.07 μmol/g liver of vitamin A represents deficient reserves	Gold standard for assessing vitamin A status Too invasive for public health studies
Isotope dilution	GCMS GCCIRMS	<0.07 μmol/g liver of vitamin A represents deficient reserves	Optimal modern standard for assessing vitamin A status Not currently feasible for public health studies due to high time and cost requirements
Serum β-carotene	HPLC	No standard thresholds established	As a measure of provitamin A, β-carotene may be useful when assessing improvements to diet
Breast milk retinol	HPLC	≤1.05 μmol/l (or ≤8 mg/g milk fat) indicative of low breast-milk vitamin A content	Only applicable for lactating women Modest response to VAS

[a]RDR, relative dose response; MRDR, modified relative dose response; GCMS, conventional gas chromatography–mass spectrometry; GCCIRMS, gas chromatography–combustion–isotope ratio mass spectrometry.

To help improve vitamin A status and reduce the burden of VAD, diet diversification and VAS have emerged as important public health interventions. VAS is typically administered orally using gelatin capsules containing 50 000–200 000 international units of vitamin A, most commonly to preschool-age children and women of childbearing age [19]. Diet diversification efforts have considered a range of strategies and foodstuffs, often adjusted for local context [20–23].

Although great progress has been achieved in recent decades, VAD remains an important cause of blindness and morbidity [24]. In 2009, the WHO estimated that night blindness affected over 5 million preschool-age children and almost 10 million pregnant women. Low serum retinol concentration (<0.70 μmol/l) was estimated to affect 190 million preschool-age children and 19 million pregnant women [9]. The geographic scope of VAD is also immense. Based on night blindness and serum retinol, 45 and 122 countries respectively suffer from VAD as a significant public health problem [9].

STH: A Disease of Poverty and the Environment

More than 1 billion people are at risk of STH, a group of diseases caused by the intestinal worms *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), hookworm (*Ancylostoma duodenale* and *Necator americanus*), and *Strongyloides stercoralis* (threadworm) [4,25]. The

global burden of STH is estimated at over 5 million DALYs, largely due to anemia, stunting, and impaired cognitive development [12,26–28]. STH remains prevalent worldwide and represents a public health problem in 106 countries [10].

Humans are infected after ingesting eggs (*A. lumbricoides* and *T. trichiura*) or through penetration of the skin by larvae in the soil (hookworm) [28]. Current control strategies have focused on preventive chemotherapy, particularly for school-age children [29]. At-risk populations receive anthelminthic agents once or twice per year, usually a single oral dose of albendazole (400 mg) or mebendazole (500 mg). Treatments are typically provided in school settings but can also be delivered through community-wide initiatives or complementary distribution platforms (e.g., child-health days) [30]. Utilizing the 'platform' of VAS to coadminister deworming medicine could reduce costs and help scale up anthelminthic drug coverage among preschool-age children [31].

STH is typically diagnosed by microscopic examination of fecal samples for helminth eggs and the WHO recommends using the Kato–Katz method [29]. Other methods, including mini-FLOTAC and molecular diagnostics using PCR, have also been utilized, each with specific advantages. A recent review of diagnostics for STH provides an overview of the performance of the different assays [32]. Methodological considerations regarding the diagnosis of STH are summarized in Table 2.

Infections are categorized into three levels of intensity – light, moderate, and heavy – based on the number of eggs per gram of feces (epg). Higher egg counts, which correspond to more intense worm burdens, are associated with greater morbidity [29].

Mechanisms to explain the adverse effects of STH infection on nutrition have been proposed and include decreased appetite and nutrient intake, impaired absorption, and increased nutrient loss or altered metabolism [4]. Specifically for VAD, *Ascaris* expresses a range of retinol-binding proteins, retinol dehydrogenases, and retinoic acid receptors that utilize retinol for growth and

Table 2. Methodological Considerations Regarding the Diagnosis of STH

Consideration	Impact	Refs
Infection intensity	STH status is often reported as simply 'infected' or 'not infected', but the intensity of the worm burden represents a more meaningful indicator Morbidity is linked with intensity of infection and many individuals with light infections do not experience obvious symptoms Most individuals in an endemic area harbor light infections, while a small proportion are heavily infected and may harbor a large proportion of the overall community worm burden Many diagnostic methods, including the Kato–Katz method, will vary in sensitivity depending on intensity of infection and species of STH	[28,32–38]
Different helminth species	The term 'soil-transmitted helminthiasis' groups together infections from multiple, distinct intestinal nematodes that share the capability to be transmitted through soil *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, *Necator americanus*, and *Strongyloides stercoralis* can differ in infection sequelae, susceptibility to current drug regimens, ease of detection, and other factors	[28,32,39,40]
Drug efficacy	Efficacy varies among different anthelmintic drugs; even a single drug will vary in efficacy against different helminths Albendazole, the most commonly used drug, yields fecal egg count reduction (FECR) rates of 99.5% for *A. lumbricoides*, 94.8% for hookworm, and 50.8% for *T. trichiura* Mebendazole yields FECR rates that also differ by helminth: 97.6% for *A. lumbricoides*, 79.6% for hookworm, and 63.1% for *T. trichiura* *S. stercoralis* infection can be particularly difficult to treat in a population context, as multiple doses or drug combinations (e.g., with ivermectin) are typically used to improve outcomes	[39–42]

development [43]. The pathways through which this occurs and their impacts on the human host remain unclear. Intestinal worms, due largely to their small biomass, consume only a small proportion of their host's dietary nourishment [44]. Other mechanisms may be more deleterious for nutrition, including helminth-induced tissue damage [45], decrease in host appetite [46], or simply increased metabolism and caloric demand resulting from the host's immune response [47]. Further, *A. lumbricoides* infection can alter the structure of the intestinal mucosa [48] and is associated with reduced fat absorption in humans [49,50] and animal models [51–54]. One trial randomized vitamin-A-deficient pigs to be infected by *Trichuris suis* and *Ascaris suum* (or serve as uninfected controls) and did not find a significant effect on either liver or serum retinol levels [55].

Inconclusive Evidence of STH Impact on Vitamin A Status

Evidence linking STH with vitamin A status is mixed. De Gier and colleagues recently conducted a meta-analysis that reviewed evidence linking helminth infections in school-age children with a range of micronutrient indicators [11]. Their comprehensive review included both experimental and observational studies of schistosomiasis or STH and numerous micronutrient markers (retinol, iron/ferritin, iodine, zinc, folate, and vitamin B12). Four randomized controlled trials (RCTs) were identified but none detected a significant difference in vitamin A status between treatment groups, which received anthelminthic agents, and control groups. A meta-analysis of 15 additional observational studies yielded a negative association between helminth infection and serum retinol (standardized mean difference: −0.30; 95% confidence interval: −0.48, −0.13) [11]. However, the observational studies exhibited strong heterogeneity, suggesting that the meta-analysis averaged multiple distinct effects rather than describing the same particular relationship between helminth infection and serum retinol.

A recent study not included in the meta-analysis by de Gier and colleagues found a significant connection between STH and VAD. In periurban slums in Kenya, both any STH infection and *A. lumbricoides* infection were associated with a greater prevalence of VAD after controlling for demographic factors and nutritional status [56].

RCTs have yielded inconclusive findings regarding the intersection of vitamin A status and STH. Tanumihardjo and colleagues conducted a randomized trial exploring the relative effects of albendazole and VAS among enrolled Indonesian children (n = 309, 0.6–6.6 years old) with *A. lumbricoides* infection [57]. Sixty percent of enrolled children had light infections (1–4999 epg), 30% had moderate infections (5000–49 999 epg), and 10% had heavy infections (≥50 000 epg). Children were randomized into six treatment regimens, including a control group, to test the separate and combined effects of deworming and VAS. Across the experimental groups, deworming alone did not have a significant effect on the dehydroretinol/retinol ratio (P = 0.37) and the statistical interaction of treatment with albendazole and vitamin A was also not significant (P = 0.75).

Another randomized trial by Reddy *et al.* [58] also investigated the additive impact of deworming on VAS and found nonsignificant results. The authors investigated a population of 487 children (age 1–5 years) with 35% *A. lumbricoides* prevalence. They found no difference in serum retinol levels for children who received VAS compared with those who received deworming medications (tetramisole) and VAS. Deworming alone also did not improve vitamin A status compared with placebo. While serum retinol can be insensitive to changes in vitamin A status, both experimental groups that received VAS showed significantly increased serum retinol levels. This suggests that the null findings for deworming were not solely caused by the use of serum retinol as the outcome measure.

Another study by Mwaniki *et al.* [59] investigated the effects of multimicronutrient supplementation and multihelminth chemotherapy on serum retinol in Kenyan schoolchildren. In a four-arm

placebo-controlled randomized study, Mwaniki and colleagues investigated the effects of daily multimicronutrient supplementation over 8 months, with or without initial treatment using single-dose albendazole (for STH) and praziquantel (for schistosomiasis), in 977 Kenyan schoolchildren (age 7–19 years). Vitamin A supplementation increased serum retinol levels; praziquantel, but not albendazole, enhanced this effect. Prevalence was 14% for *A. lumbricoides*, 45% for *T. trichiura*, 54% for hookworm, and 71% for *Schistosoma mansoni*. Although egg counts were not reported, it is likely that all *Ascaris* infections were of low intensity due to the low prevalence.

Studies measuring preformed vitamin A (e.g., serum retinol) as the primary indicator of vitamin A status in relation to STH have found minimal significant results, but there is evidence to suggest that deworming can improve absorption of provitamin A, specifically β-carotene. Haque *et al.* conducted a four-arm, placebo-controlled randomized trial in Bangladesh investigating β-carotene supplementation and deworming in 244 preschool children who were infected with *A. lumbricoides* [60]. Children received low-dose β-carotene capsules daily for 6 months, either with or without albendazole, which was provided at the beginning of the study and 4 months after. Serum β-carotene increased by 0.08 μmol/l after deworming, 0.06 μmol/l after β-carotene supplementation, and 0.21 μmol/l when treatments were combined. The increase in serum β-carotene measured in the group that received both deworming and supplementation was greater than the sum of the effects measured in both of the other groups, suggesting that a synergistic effect may be occurring with combined treatment.

There is also evidence that deworming may increase the effectiveness of food-based vitamin A interventions. A randomized study by Jalal *et al.* found that deworming improved serum retinol levels when combined with added dietary fat [61]. The combined effects of β-carotene-rich food, dietary fat, and deworming were also additive for participants with high-intensity infections. As a limitation, this study did not assess deworming separately from fat or food improvements, and those complementary interventions could confound the impact of deworming.

Beyond intervention studies, Ahmed and Mohiduzzaman did not find strong evidence linking ascariasis with malabsorption of vitamin A in humans [62]. In a study of 29 children in Bangladesh, they found that over 99% of vitamin A from supplements was absorbed successfully by the children. Only a small amount of retinol was recovered from stool samples. Expelled worms were also separated from stools and assayed, but no retinol was detected. However, there was a statistically significant negative linear relationship between the amount of vitamin A recovered from stools and worm burden. Most children in the study harbored light-intensity infections.

Concluding Remarks and Future Directions

Preformed vitamin A (i.e., retinol) has exhibited minimal or inconclusive responsiveness to deworming, but provitamin A (e.g., β-carotene) levels have increased significantly after treatment for STH. Considerations about the sensitivity and validity of serum retinol as an indicator for vitamin A status (Table 1) and the impact of STH infection intensity on disease morbidity make it difficult to interpret null findings from some trials. However, Tanumihardjo and colleagues largely account for these issues in their 1996 trial and provide the strongest evidence that treatment for STH may not improve vitamin A status directly [58]. Other motivations beyond improving vitamin A uptake may still justify coadministration of VAS with deworming.

In two studies that considered β-carotene as an indicator, Haque *et al.* and Jalal *et al.* found promising results after deworming [60,61]. As there is increased investment in sustainable dietary diversification efforts (e.g., promoting consumption of leafy green vegetables or orange-fleshed sweet potatoes) as well as mass-scale vitamin A food fortification (e.g., sugar, oil), the impact of alternative vitamin A interventions will need to be evaluated. Food fortification has

Outstanding Questions

What impact would integrated interventions have if implemented during early child development?

What is the impact of alternative vitamin A interventions, such as dietary diversification and vitamin A fortification, on vitamin A status in STH-endemic areas?

To what extent does coadministering treatment for STH and VAS increase coverage of VAS and save costs?

How should integrated STH and VAD programs be optimally monitored and evaluated?

proven to be a cost-effective strategy to address micronutrient deficiencies in developed countries and has been discussed as an important strategy for developing countries [63–66]. As evidenced by these two trials, dietary diversification to improve VAD could benefit from coadministered deworming.

Dosing of vitamin A could account for some of the discrepancy observed between the effects of STH on preformed vitamin A and provitamin A. Food fortification or diet diversification typically involve low, regular doses of vitamin A or provitamin A. High-dose supplementation with preformed vitamin A may interact differently with helminth infections. Further, most currently available data consider older, school-age children who may be less susceptible to morbidity from VAD compared with their younger peers. Additional research could examine the importance of early integrated interventions that target preschool-age children.

Other considerations may also support the value of adding deworming to current VAS efforts. No evidence has emerged indicating additional adverse effects caused by combining albendazole and vitamin A treatments. Even the large cluster-randomized Deworming and Enhanced Vitamin A (DEVTA) study found no evidence of immediate adverse events from albendazole and vitamin A treatment [67]. Further, deworming can improve participation in coadministered interventions since the results of deworming are readily observed in the stool [57]. Anthelminthic drugs appear to be popular in many communities, boosting treatment compliance and potentially increasing overall coverage of health interventions [4]. Community health volunteers also have reported that distributing deworming tablets strengthens their recognition in the community [5]. VAS cannot typically provide such clearly visible results, except in cases of xerophthalmia. Thus, deworming may strengthen the programmatic effectiveness of VAS without adding additional risks. Additional high-quality research would help facilitate a more thorough exploration of the synergy achieved by complementing VAS with deworming.

The WHO has established a target of regular deworming for at least 75% of at-risk preschool-age children by 2020 – an estimated 266 million children worldwide. In 2013, the most recent year for which data are available, global coverage as reported through the standard WHO channels was only 24% [10]. However, when UNICEF-assisted treatments coadministered with VAS were included, reported coverage increased to 49% [68]. This recent experience demonstrates the magnitude of coadministration already under way and the importance of the VAS platform for achieving the WHO deworming targets for preschool-age children.

While additional research is needed to clarify the relationship between soil-transmitted helminthiasis and vitamin A status, current evidence suggests that increasing coordination of campaigns for the two conditions represents an important opportunity that can yield significant public health benefits. However, based on existing evidence, program managers should not anticipate a significant increase in vitamin A uptake following the addition of deworming to VAS campaigns.

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